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Case Report

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A case of dapsone-induced hemolytic anemia related to G6PD enzyme deficiency

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ABSTRACT

Hemolytic anemia is characterized by a decrease in the number of circulating erythrocytes due to an increase in their hemolysis. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common erythrocyte enzyme defects related to hemolysis. The G6PD enzyme abrogates the hemolysis of erythrocytes by protecting them against oxidative stress due to its involvement in the glutathione metabolism. G6PD enzyme deficiency-related hemolytic anemia may present as neonatal jaundice or become manifest due to exposure to infections, favism and medications later in life. Dapsone is a medication that is preferred by doctors in the treatment of many dermatological disorders such as pemphigus vulgaris, and leads to hemolysis in the presence of G6PD enzyme deficiency. In this type of non-immune hemolysis, haptoglobulin is low and Coombs' tests are negative. Hemolytic anemia, a serious complication that may appear subsequent to dapsone use, can be prevented by testing G6PD enzyme levels prior to dapsone therapy. In this case, we emphasized that the hemolytic anemia in the patient using dapsone may be due to G6PD enzyme deficiency.

Keywords: Dapsone, glucose-6-phosphate dehydrogenase, hemolytic, anemia

INTRODUCTION

Hemolytic anemia defines a group of anemias occurring due to the shortening of normal red blood cell (RBC) lifespan due to factors extrinsic to RBCs or structural changes in RBCs (1). As a result of the increase in RBC hemolysis, anemia and associated clinical symptoms become manifest. Hemolytic anemias can be categorized under two broad titles: hereditary and acquired. Here, we present a case diagnosed with pemphigus vulgaris who was determined to have Glucose-6-phosphate dehydrogenase (G6PD) deficiency based on the tests performed subsequent to hemolytic anemia that occurred during dapsone therapy.

CASE

66 year-old female patient presented to the dermatology polyclinic with raised erythema and bullous lesions in a butterfly distribution on the face involving the eyelids (**Figure 1**). The patient was diagnosed with pemphigus vulgaris based on punch biopsy and, as treatment, was started on 2x50 mg dapsone (PO), 1x16 mg methylprednisolone (PO) and corticosteroid pomades. Blood parameters at diagnosis were as follows: leukocyte, 8.1×10^9/L (4.4-11); hemoglobin (Hgb), 12.3 gr/dl (12-16); thrombocyte, 270×10^9/L (142-424); MCV, 86 fl (80-100); LDH, 210 U/L (135-214); ALT, 22 U/L (0-33); AST, 16 U/L (0-32); direct bilirubin, 0.5 mg/dl (0-0.3); indirect bilirubin, 0.8 mg/dl (0.1-0.9); creatinine, 0.59 mg/dl (0.5-0.9); folate, 10 ng/ml (5.4-24); vitamin B12, 310 ng/ml (210-910). The patient presented to the dermatology polyclinic 6 days after the onset of treatment due to fatigue, pallor, icterus of the sclerae. The patient was referred to the hematology polyclinic based on the following test results: Hgb, 3.8 gr/dl; leukocyte, 11×10^9/L; thrombocyte, 222×10^9/L; MCV, 108 fl; creatinine, 0.8 gr/dl; LDH, 810 U/L; indirect bilirubin, 6.4 mg/dl; direct bilirubin, 0.8 mg/dl.

The patient's history and anamnesis did not include a similar condition that followed medication use or an operation. On physical examination; sclerae were icteric, skin was pale, and there was no organomegaly or peripheral lymphadenopathy. In addition, urine was dark in color. On peripheral blood smear; macrocytosis, anisocytosis-poikilocytosis, polychromasia and Heinz bodies were observed (**Figure 2**). Corrected reticulocyte was determined as 5.2% (0.5-2%); ANA, anti-dsDNA, direct Coombs (IgG) and indirect Coombs' tests were negative. The haptoglobulin level was determined as 8 mg/dl (30-200) and was below the reference range. As

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the present hemolytic anemia picture was reasoned to be associated with dapsone, the medication was stopped and 16 mg methylprednisolone was started. No pathological findings were determined on abdominal ultrasonography and lung radiography. Based on the perception that anemia was associated with dapsone, G6PD enzyme levels were examined. The patients' G6PD level was found as 3.52 IU/gHb (7.48-10.20 IU/gHb), and was below the reference. During follow-up, fatigue, subicterus and pallor improved. Hgb levels increased, LDH and indirect bilirubin levels showed a gradual decrease. Blood parameters after 10 days were as follows: Hgb 11,8, gr/dl; leukocyte, 7.6×10^9/L; thrombocyte, 234×10^9/L; MCV, 98 fl; creatinine, 0,6 gr/dl; LDH, 260 U/L; direct bilirubin, 0.42 mg/dl; indirect bilirubin, 0.44 mg/dl.

Figure 1. Raised erythematous and bullous lesions on the face, in a butterfly-wing pattern involving the eyelids

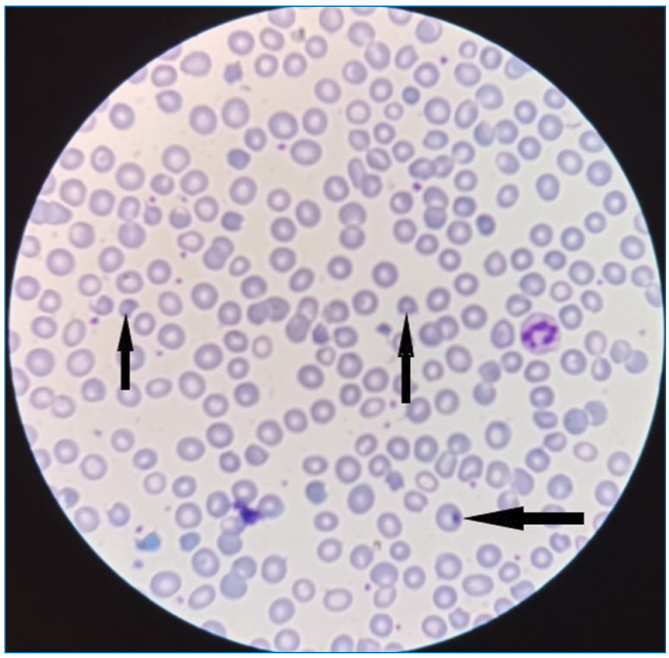

Figure 2. Peripheral smear: macrocytosis, anisocytosis-poikilocytosis, polychromasia and heinz body

DISCUSSION

G6PD enzyme deficiency is hereditary and constitutes one of the causes of metabolic disorder-related hemolytic anemia. It is the most common erythrocyte enzyme deficiency and is more prevalent among males due to its X-linked recessive inheritance (2). It is estimated that this disease affects 400 million individuals worldwide (3). The prevalence of G6PD enzyme deficiency is 0.5% in the general Turkish population, and 8.2% in the Cukurova region (4). The G6PD enzyme is the most important enzyme that protects RBCs against oxidant stress. RBCs are protected against oxidative stress by the production of NADPH, a co-factor of glutathione reductase that reduces glutathione, in the pentose phosphate pathway. In G6PD deficiency, NADPH decreases, and therefore, glutathione reductase levels fall, making the erythrocytes more sensitive to oxidative stress and causing them to be hemolyzed (5). G6PD becomes manifest as neonatal jaundice in 30% of the cases (5). The remaining subsection of the cases become clinically manifest later in life when exposed to oxidative stress due to dapsone, antimalarial medication, infections, operations, as well as consumption of fava, soybeans and fava beans (6). Dapsone is an aniline derivative that belongs to the synthetic dapsone group, and is a sulfone-group antibiotic with both antibacterial and anti-inflammatory effects that inhibits folate synthesis. Dapsone sometimes decreases the oxidation of hemoglobin by inhibiting the hemoglobin reductase enzyme found in the RBC. This effect is more marked in the presence of G6PD enzyme deficiency, and the most common side effects associated with this condition are methemoglobinemia and hemolysis (7). These side effects become more marked in correlation with the G6PD enzyme deficiency (7).

Dapsone is preferred by dermatologists in the treatment of diseases such as lepra, pemphigus vulgaris, pyoderma gangrenosum, bullous lupus erythematosus, bullous pemphigoid, linear IgA dermatosis, aphthous ulcers, lupus panniculitis and dermatitis herpetiformis (7). In our patient, whose G6PD deficiency was unknown, hemolytic anemia occurred after the onset of dapsone therapy for pemphigus vulgaris. Autoimmune hemolytic anemia is an immunologic condition characterized by RBC breakdown induced by antibodies that bind to erythrocyte surface antigens (8). Drug-related autoimmune hemolytic anemia is a condition that occurs due to the interaction between the erythrocyte membrane and the immune system (9). Anti-drug antibodies bind to the medication that is adsorbed and weakly bound to the erythrocyte membrane. Further, antibodies produced in response to medication in the circulation result in an antigen-antibody complex. This complex causes hemolysis by either adsorbing on to the erythrocyte membrane or inducing the complement cascade (10). Based on the occurrence of hemolytic anemia following dapsone use, the presence of negative Coombs' test results and the subsequent detection of G6PD enzyme deficiency in our patient, we were able to exclude drug-related autoimmune hemolytic anemia.

The treatment of G6PD enzyme deficiency-related hemolytic anemia, is avoidance of medications, and conditions such as infections and favism that result in oxidant stress. A blood transfusion may be performed if the Hgb level is below 7 gr/dl, or if it is between 7-9 gr/dl with symptoms or hemoglobinuria (10). In the case of our patient, we stopped dapsone and transfused the patient with 2 units of erythrocyte suspension as her Hgb level was 3.8 gr/dl. Blood parameters spontaneously recovered during follow-up.

CONCLUSION

Dapsone is used widely in the treatment of various disorders, most notably, dermatological disorders. In G6PD deficiency, using dapsone is risky and is associated with a high probability of hemolytic anemia occurrence. In this case presentation, we aimed to stress that hemolytic anemia encountered in a patient on dapsone would be linked to G6PD enzyme deficiency.

ETHICAL DECLARATIONS

Informed Consent: Permission was obtained from the patient for the use of the image, and signed informed consent was obtained.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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